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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,080	10/08/2004	J. Phillip Bowen	B40-002	3420

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EXAMINER	
GULLEDGE, BRIAN M	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,080	BOWEN ET AL.	
	Examiner	Art Unit	
	Brian Gulledge	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40 and 51-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40 and 51-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Previous Rejections

Applicants' arguments, filed 15 March 2010, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The examiner has altered his previous position regarding enablement. While unusual, this is permitted so long as the rules of Patent Office practice are duly complied with an applicant has no legal ground for complaint because of such change in view. *In re Ruschig*, 154 USPQ 118, 120-21 (CCPA 1967). Nevertheless, the delay in prosecution is regretted.

Claim Objections

Claims 50 and 51 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. These claims each just repeat the identical options for the tumor and cancer, respectively, which are recited by instant claim 40.

Claim Rejections - 35 USC § 112, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40 and 51-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

The nature of the invention, state and predictability of the art, and relative skill level: The invention relates to methods of treating either tumor or cancers in patients in need thereof using one of two entiomeric compounds. The tumors are limited to neurofibromatoses, tuberous sclerosis, and hemangiomas, whereas numerous cancers are recited. The relative skill of those in the art is high, that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Johnson et al. (*British Journal of Cancer*, **2001**, 84(10), pages 1424-1431), Voskoglou-Nomikos et al. (*Clinical Cancer Research*, **2003**, *9*, pages 4227-4239), and Suggitt et al. (*Clinical Cancer Research*, **2005**, *11*, pages 971-981), each discussed in turn below.

Johnson et al. analyzes the relationship between drug activity in NCI preclinical *in vitro* and *in vivo* models and early clinical trials. For 39 agents with both xenograft data and Phase II clinical trial results available, *in vivo* activity in a particular histology in a tumor model did not closely correlate with clinical activity in the same human cancer histology (Abstract; page 1426, right column, "Indicators of clinical activity"). This teaching casts doubt on the correspondence of the pre-clinical models to clinical results, i.e., unpredictability. In contrast, when a compound is found to be active in at least one-third of tested xenograft models, there was a correlation with

ultimate activity in at least some Phase II clinical trials (Abstract). With respect to *in vitro* cell proliferation assays, while these assays are somewhat predictive of likely xenograft activity in lung or breast xenograft models, no predictive value is found with other histologies, thus casting doubt on the likelihood that a drug showing efficacy *in vitro* will necessarily have efficacy *in vivo* (xenograft models), let alone clinically (paragraph bridging pages 1427-1428; Tables 3A and 3B). In conclusion, Johnson et al. state that a histology to histology comparison of xenograft versus clinical results cannot be reliably discerned and with the exception of lung, histological matches were not found between *in vivo* models and clinical response although activity in multiple xenografts does appear to predict for some degree of clinical efficacy (page 1430, left column, "Discussion").

Voskoglou-Nomikos et al. look at the value of three preclinical cancer models, the *in vitro* human cell line, the human xenograft, and the murine allograft, to examine whether they are reliable in predicting clinical activity. The relevance of tumor type-specific preclinical results for the corresponding human cancers in the clinic can be viewed using two different approaches: 1) compound-oriented, where a drug is assumed to have potential activity against all human tumor types if it is effective against a single tumor test type; and 2) disease-oriented, where a drug with preclinical activity in a single tumor type would only be expected to be effective in the same tumor type in patients (page 4227, right column, second paragraph under "Introduction"). Looking now to the results, the *in vitro* model was found to be predictive of Phase II clinical performance for NSCLC under the disease-oriented approach (i.e., efficacy in the NSCLC *in vitro* cell proliferation assay correlated to Phase II efficacy in NSCLC, but not other cancers). The same model was predictive in breast and ovarian cancers under the compound-oriented

approach (i.e., if a compound was effective against breast or ovarian cancer in vitro, it was effective clinically against the tested cancer types, but, interestingly, not breast or ovarian cancer) (paragraph bridging pages 4235-4236). With respect to the predictive value of human xenograft models, these models showed good tumor-specific predictive value for NSCLC and ovarian cancer when panels of xenografts were used. However, the xenograft models failed to predict clinical performance both in the disease and compound-oriented setting for breast and colon tumors (page 4236, right column, first paragraph). In conclusion, Voskoglou-Nomikos et al. state that their results suggest that the *in vitro* human tumor cell line and the human tumor xenograft models might have predictive value in some solid tumors (such as ovary and NSCLC) under both the disease and compound-oriented approaches, as long as an appropriate panel of tumors is used in preclinical testing (page 4237, left column, fourth paragraph).

Suggitt et al. teach that the number of anticancer agents that fail in the clinical far outweighs those considered effective, suggesting that the selection procedure for progression of molecules into the clinic requires improvement (Abstract). This review article provides information regarding the progression of preclinical anticancer drug screening from the 1950s through early 2000s. With regard to models used today, the NCI 60-cell *in vitro* cell line screen used since the mid-80s, while a simple, relatively fast, cheap, and reproducible method of providing indicative data of mechanistic activity and target interaction, the *in vitro* methods used therein are susceptible to false-positive and false-negative results (page 973, right column, first full paragraph). Also, factors other than the inherent chemosensitivity of tumors cells significantly influence the outcome of chemotherapy *in vivo* (e.g., pharmacokinetics, tumor microregions/pH, and pO2). Such factors are not represented in the *in vitro* assay (*id.*). In other

words, while *in vitro* screening methods are useful in selecting compounds for secondary, more comprehensive, *in vivo* testing, they cannot reliably be used to predict in vivo activity.

Also discussed in this review is the "hollow fiber assay" which assesses the pharmacologic capacity of compounds to reach two physiologic compartments within the nude mouse and shows a practical means of quantifying viable tumor cell mass (page 973-974, "The Hollow Fiber Assay"). Results of human tumor xenograft studies are discussed on pages 974-975. Of note, this review article indicates that many compounds have shown promising activity in *s.c.* xenograft models, progressed to the clinic and revealed disappointing results (page 974, right column). Further, despite enormous efforts to discover new chemotherapeutic drugs for treating the most common cancers, the conventional murine and xenograft test systems have identified only a limited number of useful agents that are clinically effective at well-tolerated doses (*id.*). Despite the relatively limited value of xenograft models in predicting clinical efficacy, the authors do point out the benefit that these models have if xenografts are derived from actual patient biopsies and characterized to ensure that a particular molecular target is expressed (e.g., a molecular target of the drug being studied) (page 975, left column). Finally, this review discusses orthotopic and metastasis tumor models, autochthonous models, and genetically engineered cancer models (pages 975-978). These are relatively new models that are not used by many labs and few studies have documented the use of these models in cancer therapy and in predicting clinical response. In order to assess the predictive value of these models, "preclinical studies testing currently used chemotherapeutic agents are required" (page 977, right column).

The breadth of the claims: The claims recite the treatment of all of the recited forms of

cancers and tumor recited by the administration of only either enantiomer of the recited compound.

The amount of direction or guidance provided and the presence or absence of working examples: The specification provides no direction or guidance for practicing the claimed invention. No reasonably specific guidance is provided concerning useful therapeutic protocols for treating these cancers is provided. The specification discloses that a dose of 3 μg/mL of one of the two enantiomers claimed inhibits cell growth of SVR cells, which are used to screen for angiogenesis inhibitors. The figure also shows that either a dose of 1 μg/mL or a dose of 6 μg/mL also inhibits cell growth of SVR cells. It is unclear which bars of the data presented correlate to each dose. The other dose has either no effect or stimulates growth, and it is unclear which due to the lack of error bars. The specification, however, provides no data regarding the use of the claimed compounds to treat tumors or cancers, either *in vitro* or *in vivo*.

The quantity of experimentation necessary: Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to treat the recited tumors and cancers in a human patient as inferred by the claim and contemplated by the specification. The above cited and discussed articles took known, clinically effective anticancer drugs and retrospectively looked at their preclinical *in vitro* and *in vivo* efficacy: however, the *in vitro* and *in vivo* models of cancer could not be used to accurately predict whether a drug effective in preclinical models would be clinically useful in the treatment of cancer. Thus, it does not appear that preclinical *in vitro* and *in vivo* anticancer models can reliably predict the clinical efficacy of a known anticancer drug. In view of this fact, it would appear that these models cannot be used

to predict the clinical activity of a genus of compounds that has never been administered to a human patient. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no reasonable expectation of success.

Claim Rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 52 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims limit the cancer to a list of species, including kidney cancer. Claim 40, from which these claims depend, limits the cancers to those selected from a particular list, but the species disclosed do not include kidney cancer. Thus, claims 52 and 53 recite options outside of the breadth of claim 40, and it is unclear which listing of cancers applies to the claimed method.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Gulledge whose telephone number is (571) 270-5756. The examiner can normally be reached on Monday-Thursday 6:00am - 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BMG

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